

João Pedro Alves Nunes Pereira

Canabinóides sintéticos: farmacocinética, farmacodinâmica e implicações  
clínicas e forenses / Synthetic cannabinoids: pharmacokinetics,  
pharmacodynamics and clinical and forensic issues

março, 2017

João Pedro Alves Nunes Pereira

Canabinóides sintéticos: farmacocinética, farmacodinâmica e implicações  
clínicas e forenses / Synthetic cannabinoids: pharmacokinetics,  
pharmacodynamics and clinical and forensic issues

**Mestrado Integrado em Medicina**

**Área: Medicina Legal**

**Tipologia: Monografia**

**Trabalho efetuado sob a Orientação de:**

**Doutor Ricardo Jorge Dinis Oliveira**

**E sob a Coorientação de:**

**Professor Doutor Félix Carvalho**

**Trabalho organizado de acordo com as normas da revista:**

**Forensic Science International**

março, 2017

**FMUP**

Eu, gões Pedro Alves Nunes Pereira, abaixo assinado, nº mecanográfico 201101343, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 20 / 3 / 2017

Assinatura conforme cartão de identificação:

gões Pedro Alves Nunes Pereira

NOME

João Pedro Alves Nunes Pereira

NÚMERO DE ESTUDANTE

E-MAIL

201101343 jpnunes@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina Legal

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Constituintes sintéticos: farmacocinética, farmacodinâmica e implicações clínicas e forenses

ORIENTADOR

Doutor Ricardo Jorge Dinis-Oliveira

COORDINADOR (se aplicável)

Professor Doutor Felix Carvalho

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTES TRABALHOS APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	<input checked="" type="checkbox"/>
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTES TRABALHOS (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	<input type="checkbox"/>
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTES TRABALHOS.	<input type="checkbox"/>

Faculdade de Medicina da Universidade do Porto, 20/3/2017

Assinatura conforme cartão de identificação:

João Pedro Alves Nunes Pereira



## **DEDICATÓRIA**

Ao meu pai,  
à minha mãe, à minha irmã,  
a toda a restante família e aos meus amigos.

**Full Title:** SYNTHETIC CANNABINOIDS: PHARMACOKINETICS, PHARMACODYNAMICS AND CLINICAL AND FORENSIC ISSUES

**Running Head:** synthetic cannabinoids

Authors' names and institutional addresses:

João Pedro Pereira<sup>1</sup>, Félix Carvalho<sup>2</sup>, Ricardo Jorge Dinis-Oliveira<sup>1,2,3\*</sup>

<sup>1</sup>Department of Legal Medicine and Forensic Sciences, Faculty of Medicine, University of Porto, Porto, Portugal.

<sup>2</sup>UCIBIO, REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal.

<sup>3</sup>IINFACTS - Institute of Research and Advanced Training in Health Sciences and Technologies, Department of Sciences, University Institute of Health Sciences (IUCS-CESPU), Gandra, Portugal.

\*Corresponding authors:

João Pedro Pereira

Email: [mimed11264@med.up.pt](mailto:mimed11264@med.up.pt)

Félix Carvalho

Email: [felixdc@ff.up.pt](mailto:felixdc@ff.up.pt)

Ricardo Jorge Dinis-Oliveira

Email: [ricardinis@med.up.pt](mailto:ricardinis@med.up.pt)

Department of Legal medicine and Forensic Sciences

Faculty of Medicine, University of Porto

Alameda Prof. Hernâni Monteiro,

4200-319 Porto, Portugal

Phone: 00351 225513600

## ABSTRACT

Synthetic cannabinoids (SC) are a large group of chemical compounds that interact with the endocannabinoid system with the purpose of producing similar effects to the natural *Cannabis* products. However, they present more serious and unpredictable side effects, having a strong connection to the onset of acute psychosis in previously healthy individuals, to dependence and abstinence syndrome, and also to serious medical problems due to the inexistence of a specific treatment, which may culminate in death. Their identification in biological samples is carried out by complex processes only accessible in some laboratories, not being detected in routine toxicological tests accessible in medical facilities. This work aimed to review the current literature related to this subject as a way of better understanding these substances, their effects and how hard is to diagnose and consequently treat an acute intoxication in an ER. In the near future, it is necessary to develop an effective screening test to use in any ER, improve the legislation related to these substances and also discourage their consumption.

**Keywords:** synthetic cannabinoids; legal highs; spice; cannabinoid receptors; psychosis; adverse effects.

## INTRODUCTION

Synthetic cannabinoids (SC), also known as Spice, K2, among many others, have gained popularity since 2004, when they emerged as a new type of recreational drug for their psychostimulant properties, along with several other substances, commonly known as “legal highs” being attractive for their low cost and easy access through the internet or “smart shops” (Seely et al., 2012). These are lab produced cannabinoid receptors agonists, originally developed in the 60s to study the pharmacological effects related to activation of this type of receptors (Pertwee, 2006). As SC began to be used as clandestinely produced recreational drugs, they appeared in the form of smoking herbal blends, advertised as incense/potpourri and not appropriate for human consumption (Seely et al., 2011).

However, the dried plants present in these blends have no psychotropic effect in most cases, just giving the illusion of being of natural origin, being no more than mere vehicles

for the SC initially dissolved in a solvent such as acetone or ethanol. This solvent subsequently evaporates while SC stay attached to the plants, often in very different concentrations within the same package (originating parts where the concentration of SC is very high, called “hot spots”) (Fattore and Fratta, 2011; Vandrey et al., 2012).

The unpredictable toxicity of these drugs, when compared to natural *Cannabis* does not only depend of these so called “hot spots”. In addition to this, the constant change in the SC types that happen in order for these products to be kept just outside the law, the presence of more than one type of SC in each herbal blend as well as the addition of other substances (such as drugs, rat poison or embalming products) all lead to the fact that even the most experienced user does not know what is consuming, often with disastrous consequences (Dresen et al., 2010; Fattore and Fratta, 2011; National Institute on Drug Abuse, 2016). Indeed, beyond the desired euphoria effect, these compounds may cause severe psychological and physical adverse effects and even death (Tait et al., 2016). Low socioeconomic status may favor the abuse of SC (Joseph et al., 2016).

This article aims to review the state-of-the-art literature about SC, particularly its chemical structure and presentation forms, pharmacokinetics and pharmacodynamics, detection and management of acute intoxication.

## **METHODS**

An exhaustive literature search was carried out in PubMed (U.S. National Library of Medicine), without a limiting period, to identify relevant articles. “Synthetic Cannabinoids” and “Cannabimimetics” were used as search keywords . Furthermore, electronic copies of the full papers were obtained from the retrieved journal articles as well as governmental, European committees’ and UN documents and then further reviewed to find possible additional publications related to synthetic cannabinoids.

## **CHEMICAL STRUCTURE AND PRESENTATION FORMS**

SC are a large group of compounds (over 160 have been identified) with similar action to  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) molecule, though many of them being more potent than  $\Delta^9$ -THC because they are full agonists of cannabinoid receptors, while  $\Delta^9$ -



THC is partial agonist. Thus, SC present greater affinity and longer retention time to the receptors (Castaneto et al., 2014; EMCDDA, 2015).

Their naming is difficult to understand, often being assigned an abbreviation of the person who identified them at first, such as JWH compounds named after John W. Hoffman, or the place where they were discovered, as HU compounds which were discovered at the Hebrew University or even according to their chemical structure, as APICA, deriving from its long chemical name N-(1-**a**damantyl)-1-**p**entyl-1H-**i**ndole-3-**c**arbox**a**mide (Table 1) (EMCDDA, 2015; 2016; Seely et al., 2012).

Most SC are lipophilic, nonpolar and consist of about 20-26 carbon atoms, which makes them volatile when smoked with a side chain of 4-9 saturated carbon atoms being a common finding in these compounds (Figure 1) (EMCDDA, 2015).

The smoking herbal blends containing SC are sold in aluminum foil sachets with appealing images and exotic names, containing about 3g of dried herbs sprayed with the active substances (Johnson et al., 2011). As already mentioned, the active substances of these blends are always changing according to the law (Brents and Prather, 2014). If in the beginning JWH-018, JWH-073 and CP-47 were the most identified compounds, their prohibition in many countries has encouraged the creation of new compounds through small molecular changes, with the disappearance of the former SC (Hudson and Ramsey, 2011).

## **PHARMACOKINETICS**

After being smoked (their main administration form) SC reach peak blood concentration very quickly, then being redistributed to other tissues such as the brain, as demonstrated by a human study in which two individuals smoked 50µg/kg of JWH-018, reaching a blood peak concentration of 10µg after 5 minutes then quickly decreasing in the following 3h, becoming barely traceable after 24 hours (Teske et al., 2010).

It was shown that SC undergoes oxidation by cytochrome P450 enzymes (CYP) to several hydroxyl metabolites in humans, with intestinal CYP2C9 being very important when they were orally ingested, while CYP1A2 was the most abundantly expressed enzyme in the lungs, being the main form when CS are smoked (Figure 2) (Chimalakonda et al., 2012; Fantegrossi et al., 2014). Another P450 isoform, CYP2D6 also appeared to demonstrate an important role by being very active in brain areas with high expression of

CB<sub>1</sub> receptor, possibly responsible for the SC concentrations in the brain (Fantegrossi et al., 2014).

Metabolites are mostly excreted in the urine (with a small part excreted in the feces) and the presence of high urinary levels of SC glucuronide metabolites shows that the final metabolic process is the conjugation with glucuronic acid. UDP-glucuronosyltransferase enzymes (UGT), namely UGT1A3 and UGT2B7 are the most important enzymes to the presence of these final SC metabolites in the urine, with them possibly also being relevant for SC concentrations in the brain as it was hypothesized for CYP2D6 (Chimalakonda et al., 2012; Fantegrossi et al., 2014).

It has also been shown that certain SC, like AM-2201, are metabolized originating other known compounds such as JWH-018 and JWH-073, which has made difficult task of the identification of the initially consumed compound even more challenging, as we shall see ahead (Jang et al., 2014).

## PHARMACODYNAMICS

SC are high affinity full agonists of the cannabinoid receptors 1 and 2, while  $\Delta^9$ -THC of natural *Cannabis* is just a partial agonist (Castaneto et al., 2014). Both are G protein-coupled receptors, whose stimulation result in neuronal hyperpolarization and decreased neurotransmitter release, and are mostly expressed in the central nervous system such as cerebral cortex, hippocampus, basal ganglia, cerebellum and hypothalamus, even though also being present in many other tissues (Ameri, 1999; Castaneto et al., 2014; Pertwee, 1997). CB<sub>1</sub> receptors are responsible for the psychotropic effects of these, commonly known as cannabinoid tetrad (hypothermia, analgesia, catalepsy and locomotor deletion), also appearing in the peripheral nervous system (Castaneto et al., 2014; Mechoulam and Parker, 2013; Pertwee, 1997). There is not much knowledge regarding CB<sub>2</sub> receptors but it is known that they are predominantly expressed in lymphoid organs and cells of the immune system, with their stimulation having immunomodulatory effects (Pertwee, 1997).

However, it still remains unclear why SC have such distinct adverse effects from natural *Cannabis*. One hypothesis is that several of their metabolites continue to show high affinity and activation capacity of the receptors, unlike  $\Delta^9$ -THC (Fantegrossi et al., 2014; Rajasekaran et al., 2013). Another one is that they can act on different receptors, as

demonstrated by a study in which SC CP-55,940 increased responsiveness and expression of serotonergic receptor 5-HT<sub>2A</sub>, which may explain the higher anxiogenic and hallucinogenic potential of these substances, since the same mechanism occurs when some psychedelic drugs are used, such as LSD (Chiu et al., 2014; Franklin and Carrasco, 2013).

Symptoms arising from the use of SC can range from a few minutes to several days, in more extreme cases (Berry-Caban et al., 2013; Spaderna et al., 2013; Winstock and Barratt, 2013). In addition to the euphoric effect by which these substances are pursued, less desirable adverse effects may arise, such as chest pain, tachycardia, hypertension, agitation, nausea, emesis, weakness or, in more severe cases, cardiac arrhythmias, myocardial infarction, acute renal failure, respiratory depression, flaccid paralysis, rhabdomyolysis, seizures and even death cases are described as resulting from the direct action of SC (Heath et al., 2012; Lisi, 2014; National Institute on Drug Abuse, 2016; Patton et al., 2013; Tait et al., 2016). Although death may occur as a result of intoxication by SC, as it was shown by two different case reports on which the main event that led to the passing of the two young men was cardiac arrest shortly after smoking MDMB-CHMICA, the most common side effects reported are tachycardia, agitation and nausea (Adamowicz, 2016; Tait et al., 2016; Westin et al., 2016).

One of the main problems regarding the use of these drugs is its strong link to the risk of developing acute psychosis with hallucinations and schizophrenia, not only in predisposed individuals but also in previously healthy individuals (Every-Palmer, 2011; Fattore, 2016; Forrester et al., 2012; Oluwabusi et al., 2012). One explanation for these events being considerably more common with SC than *Cannabis* is the fact that these not present cannabidiol (CBD), which is thought to be a psychosis-protector molecule, in their composition unlike *Cannabis* and that makes the proven interaction between cannabinoids and dopaminergic pathways with their stimulation stronger than with *Cannabis*, possibly contributing to this increased chance of psychosis (Kuepper et al., 2013; Leweke et al., 2012).

Acute ischemic stroke was reported in two young women who developed facial and hemibody weakness after smoking “K2”. A 32 year old woman had repeated thrombosis (two kidney infarcts, pulmonary emboli and an ischemic stroke over 9 months) that only stopped when she quit smoking SC. Another case was one of a 31 year old woman who developed toxic leucoencephalopathy after repeatedly inhaling “Buzz Juice” over two days (Bernson-Leung et al., 2014; Kak et al., 2016; Raheemullah and Laurence, 2016).

There is evidence pointing to the development of tolerance and abstinence after the consumption of SC, as demonstrated by a study, in which a young man consuming “Spice Gold” continuously for 8 months, in order to feel the same effects, was increasing his daily dose up to 3g per day (Zimmermann et al., 2009). The same young man, when appealed to the doctor due to adverse effects, ceased consumption and quickly developed drug cravings, diaphoresis, hypertension, headache, agitation and nightmares (Zimmermann et al., 2009).

## **TOXICOLOGICAL ANALYSIS**

Given the increased number emergency room presentations related to SC intoxications there always was an urge to find a quick and easy method of identifying these compounds or their metabolites, especially in biological samples such as hair, blood, saliva or urine, even though that at the moment the available toxicological screens in hospitals are still not able to detect them (Dresen et al., 2010; Hudson and Ramsey, 2011).

The detection itself is done only in a few laboratories and by complex processes such as liquid chromatography mass spectrometry (LC-MS/MS), gas chromatography mass spectrometry (GC/MS), matrix-assisted laser absorption / ionization time of flight mass spectroscopy (MALDI-TOF), direct analysis in real spectrometry time (DART-MS) or immunoassays, not being relevant in clinical decision making due to their duration (Castaneto et al., 2015; EMCDDA, 2015; Znalezionna et al., 2015).

In an autopsy of a 41-year-old woman who quickly died of coronary arterial thrombosis after smoking ‘Mojo’, an SC containing herbal blend, ADB-FUBINACA was the only SC detected in a postmortem blood sample and the cause of death was considered a consequence of that consumption. In another case, 5F-PB-22 was found in the postmortem iliac blood of an 18-year-old male who was found dead after a night of partying with friends, with bilateral pulmonary and abdominal organs congestion being observed at autopsy. In both cases, autopsy blood specimens were extracted by a liquid–liquid extraction at pH 10.2 into a hexane–ethyl acetate mixture and analyzed by LC–MS-MS method (Behonick et al., 2014; Shanks et al., 2016).



## **TREATMENT OF INTOXICATIONS**

There are no specific therapeutics to CS intoxication, being an expectant attitude and supportive treatment adopted, very commonly proceeding to volume expansion by administration of intravenous fluids, being benzodiazepines also widely used for the control of agitation and more severe cases may require intubation and mechanical ventilation (Table 2) (Castellanos and Thornton, 2012; Cooper, 2016). Upon acute psychosis presentation, antipsychotic drugs may be used (Cooper, 2016). Other symptoms may receive a more directed therapy, with rapid resolution of the case most times (National Institute on Drug Abuse, 2016).

## **FINAL REMARKS**

The low prices, easy access and the false characterization of “legal highs” led to SC becoming very desirable and searched drugs mainly by young people. This has become a serious problem, in both medical and legal terms. Fortunately, many countries already have an aggressive legal approach to the emergence of these substances, making them forbidden at the time of their identification. The information dissemination about potential adverse effects made by the media, with the presentation real cases also helped to cause a lack of interest towards these drugs. In the future, it would be important to invest in the development of an easily accessible and fast detection test in all hospitals for more effective therapeutic decision-making, as well as the commercialization of a specific antidote for these harmful substances. Moreover, further studies are required to clarify interactions with other co-consumed substances. Indeed, registered signs and symptoms associated with the use of SC may often not result in their exclusive consumption, once they are usually used with other substances, such as alcohol, tobacco, *Cannabis*, ecstasy, opioids, cocaine, among others (Vandrey et al., 2012).

## **FINANCIAL & COMPETING INTEREST’S DISCLOSURE**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject

matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

## REFERENCES

- Adamowicz P (2016) Fatal intoxication with synthetic cannabinoid MDMB-CHMICA. *Forensic science international* **261**:e5-10.
- Ameri A (1999) The effects of cannabinoids on the brain. *Progress in neurobiology* **58**:315-348.
- Behonick G, Shanks KG, Firchau DJ, Mathur G, Lynch CF, Nashelsky M, Jaskierny DJ and Meroueh C (2014) Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22. *Journal of analytical toxicology* **38**:559-562.
- Bernson-Leung ME, Leung LY and Kumar S (2014) Synthetic cannabis and acute ischemic stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* **23**:1239-1241.
- Berry-Caban CS, Ee J, Ingram V, Berry CE and Kim EH (2013) Synthetic cannabinoid overdose in a 20-year-old male US soldier. *Substance abuse* **34**:70-72.
- Brents LK and Prather PL (2014) The K2/Spice phenomenon: emergence, identification, legislation and metabolic characterization of synthetic cannabinoids in herbal incense products. *Drug metabolism reviews* **46**:72-85.
- Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S and Huestis MA (2014) Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug and alcohol dependence* **144**:12-41.
- Castaneto MS, Wohlfarth A, Desrosiers NA, Hartman RL, Gorelick DA and Huestis MA (2015) Synthetic cannabinoids pharmacokinetics and detection methods in biological matrices. *Drug metabolism reviews* **47**:124-174.
- Castellanos D and Thornton G (2012) Synthetic cannabinoid use: recognition and management. *Journal of psychiatric practice* **18**:86-93.
- Chimalakonda KC, Seely KA, Bratton SM, Brents LK, Moran CL, Endres GW, James LP, Hollenberg PF, Prather PL, Radominska-Pandya A and Moran JH (2012) Cytochrome P450-mediated oxidative metabolism of abused synthetic cannabinoids found in K2/Spice: identification of novel cannabinoid receptor ligands. *Drug metabolism and disposition: the biological fate of chemicals* **40**:2174-2184.
- Chiu HY, Chan MH, Lee MY, Chen ST, Zhan ZY and Chen HH (2014) Long-lasting alterations in 5-HT<sub>2A</sub> receptor after a binge regimen of methamphetamine in mice. *Int J Neuropsychopharmacol* **17**:1647-1658.
- Cooper ZD (2016) Adverse Effects of Synthetic Cannabinoids: Management of Acute Toxicity and Withdrawal. *Current psychiatry reports* **18**:52.
- Dresen S, Ferreiros N, Putz M, Westphal F, Zimmermann R and Auwarter V (2010) Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. *Journal of mass spectrometry : JMS* **45**:1186-1194.
- EMCDDA (2015) 'Synthetic cannabinoids and "Spice" drug profile'.
- EMCDDA (2016) Perspectives on drugs: synthetic cannabinoids in Europe.
- Every-Palmer S (2011) Synthetic cannabinoid JWH-018 and psychosis: an explorative study. *Drug and alcohol dependence* **117**:152-157.

- Fantegrossi WE, Moran JH, Radomska-Pandya A and Prather PL (2014) Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to Delta(9)-THC: mechanism underlying greater toxicity? *Life sciences* **97**:45-54.
- Fattore L (2016) Synthetic Cannabinoids-Further Evidence Supporting the Relationship Between Cannabinoids and Psychosis. *Biological psychiatry* **79**:539-548.
- Fattore L and Fratta W (2011) Beyond THC: The New Generation of Cannabinoid Designer Drugs. *Frontiers in behavioral neuroscience* **5**:60.
- Forrester MB, Kleinschmidt K, Schwarz E and Young A (2012) Synthetic cannabinoid and marijuana exposures reported to poison centers. *Human & experimental toxicology* **31**:1006-1011.
- Franklin JM and Carrasco GA (2013) Cannabinoid receptor agonists upregulate and enhance serotonin 2A (5-HT<sub>2A</sub>) receptor activity via ERK1/2 signaling. *Synapse (New York, NY)* **67**:145-159.
- Heath TS, Burroughs Z, Thompson AJ and Tecklenburg FW (2012) Acute intoxication caused by a synthetic cannabinoid in two adolescents. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG* **17**:177-181.
- Hudson S and Ramsey J (2011) The emergence and analysis of synthetic cannabinoids. *Drug testing and analysis* **3**:466-478.
- Jang M, Yang W, Shin I, Choi H, Chang H and Kim E (2014) Determination of AM-2201 metabolites in urine and comparison with JWH-018 abuse. *International journal of legal medicine* **128**:285-294.
- Johnson LA, Johnson RL and Alfonzo C (2011) Spice: a legal marijuana equivalent. *Military medicine* **176**:718-720.
- Joseph AM, Manseau MW, Lalane M, Rajparia A and Lewis CF (2016) Characteristics associated with synthetic cannabinoid use among patients treated in a public psychiatric emergency setting. *The American journal of drug and alcohol abuse*:1-6.
- Kak M, Mikhail F, Yano ST, Guan R and Lukas RV (2016) Buzz Juice: Neurological sequelae of synthetic cannabinoids. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*.
- Kuepper R, Ceccarini J, Lataster J, van Os J, van Kroonenburgh M, van Gerven JM, Marcelis M, Van Laere K and Henquet C (2013) Delta-9-tetrahydrocannabinol-induced dopamine release as a function of psychosis risk: 18F-fallypride positron emission tomography study. *PloS one* **8**:e70378.
- Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkötter J, Hellmich M and Koethe D (2012) Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational psychiatry* **2**:e94.
- Lisi DM (2014) Designer drugs. Patients may be using synthetic cannabinoids more than you think. *JEMS : a journal of emergency medical services* **39**:56-59.
- Mechoulam R and Parker LA (2013) The endocannabinoid system and the brain. *Annual review of psychology* **64**:21-47.
- National Institute on Drug Abuse (2016) Synthetic Cannabinoids (K2/Spice).
- Oluwabusi OO, Lobach L, Akhtar U, Youngman B and Ambrosini PJ (2012) Synthetic cannabinoid-induced psychosis: two adolescent cases. *Journal of child and adolescent psychopharmacology* **22**:393-395.
- Patton AL, Chimalakonda KC, Moran CL, McCain KR, Radomska-Pandya A, James LP, Kokes C and Moran JH (2013) K2 toxicity: fatal case of psychiatric complications following AM2201 exposure. *Journal of forensic sciences* **58**:1676-1680.
- Pertwee RG (1997) Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacology & therapeutics* **74**:129-180.
- Pertwee RG (2006) Cannabinoid pharmacology: the first 66 years. *British journal of pharmacology* **147 Suppl 1**:S163-171.

- Raheemullah A and Laurence TN (2016) Repeated Thrombosis After Synthetic Cannabinoid Use. *The Journal of emergency medicine* **51**:540-543.
- Rajasekaran M, Brents LK, Franks LN, Moran JH and Prather PL (2013) Human metabolites of synthetic cannabinoids JWH-018 and JWH-073 bind with high affinity and act as potent agonists at cannabinoid type-2 receptors. *Toxicology and applied pharmacology* **269**:100-108.
- Seely KA, Lapoint J, Moran JH and Fattore L (2012) Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. *Progress in neuro-psychopharmacology & biological psychiatry* **39**:234-243.
- Seely KA, Prather PL, James LP and Moran JH (2011) Marijuana-based drugs: innovative therapeutics or designer drugs of abuse? *Molecular interventions* **11**:36-51.
- Shanks KG, Clark W and Behonick G (2016) Death Associated With the Use of the Synthetic Cannabinoid ADB-FUBINACA. *Journal of analytical toxicology* **40**:236-239.
- Spaderna M, Addy PH and D'Souza DC (2013) Spicing things up: synthetic cannabinoids. *Psychopharmacology* **228**:525-540.
- Tait RJ, Caldicott D, Mountain D, Hill SL and Lenton S (2016) A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clinical toxicology (Philadelphia, Pa)* **54**:1-13.
- Teske J, Weller JP, Fieguth A, Rothamel T, Schulz Y and Troger HD (2010) Sensitive and rapid quantification of the cannabinoid receptor agonist naphthalen-1-yl-(1-pentylindol-3-yl)methanone (JWH-018) in human serum by liquid chromatography-tandem mass spectrometry. *Journal of chromatography B, Analytical technologies in the biomedical and life sciences* **878**:2659-2663.
- Vandrey R, Dunn KE, Fry JA and Girling ER (2012) A survey study to characterize use of Spice products (synthetic cannabinoids). *Drug and alcohol dependence* **120**:238-241.
- Westin AA, Frost J, Brede WR, Gundersen PO, Einvik S, Aarset H and Slordal L (2016) Sudden Cardiac Death Following Use of the Synthetic Cannabinoid MDMB-CHMICA. *Journal of analytical toxicology* **40**:86-87.
- Winstock AR and Barratt MJ (2013) Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. *Drug and alcohol dependence* **131**:106-111.
- Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R and Schulz K (2009) Withdrawal phenomena and dependence syndrome after the consumption of "spice gold". *Deutsches Arzteblatt international* **106**:464-467.
- Znalezona J, Ginterova P, Petr J, Ondra P, Valka I, Sevcik J, Chrastina J and Maier V (2015) Determination and identification of synthetic cannabinoids and their metabolites in different matrices by modern analytical techniques - a review. *Analytica chimica acta* **874**:11-25.



## TABLES

Table 1 – Classification of sythetic cannabinoids into 7 groups (EMCDDA, 2015).

Groups	Examples
Naphthoylindoles	JWH-018 and JWH-073
Naphthylmethyindoles	JWH-175
Naphthoylpyrroles	JWH-130
Naphthylmethyindenenes	JWH-176
Phenylacetylindoles	JWH-250
Cyclohexylphenols	CP 47.497
Classical Cannabinoids	HU-210

Table 2 – Major averse effects of sythetic cannabinoids and treatment.

Adverse Events	Treatment
Psychosis, agitation, anxiety, paranoia	Benzodiazepines, antipsychotics, electrolyte replacement
Acute kidney injury	Intravenous fluid administration, dialysis
Tachycardia	Negative chronotropic agents, benzodiazepines
Myocardial infarction	Standard treatments, benzodiazepines
Seizures	Benzodiazepines, antiepileptic drugs
Hyperemesis	Hot showers, antiemetics, electrolyte/fluid replacement

## FIGURES

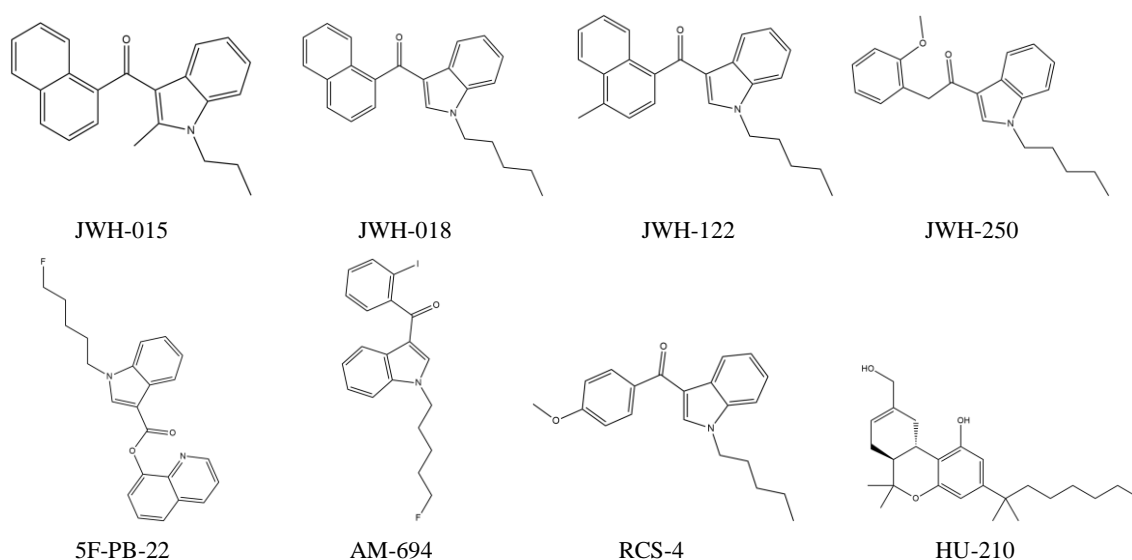
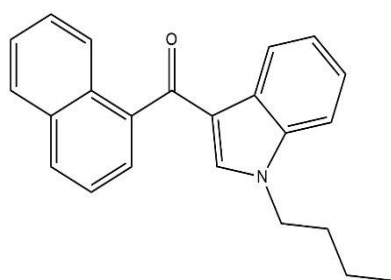
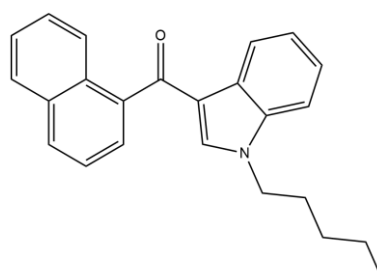


Figure 1 – Chemical structures of sythetic cannabinoids.



**JWH-073**



**JWH-018**

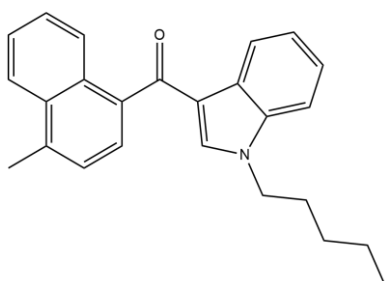
Hydroxylation

Hydroxylation

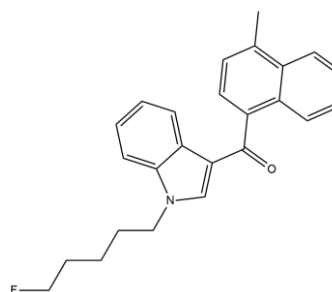
**JWH-073-N-4-OH-butyl**

Carboxylation

**JWH-073-N-butanoic acid**



**JWH-122**



**MAM-2201**

Hydroxylation

Oxidative  
defluorination

**JWH-122-N-5-OH-pentyl**

Carboxylation

**JWH-122-N-pentanoic acid**

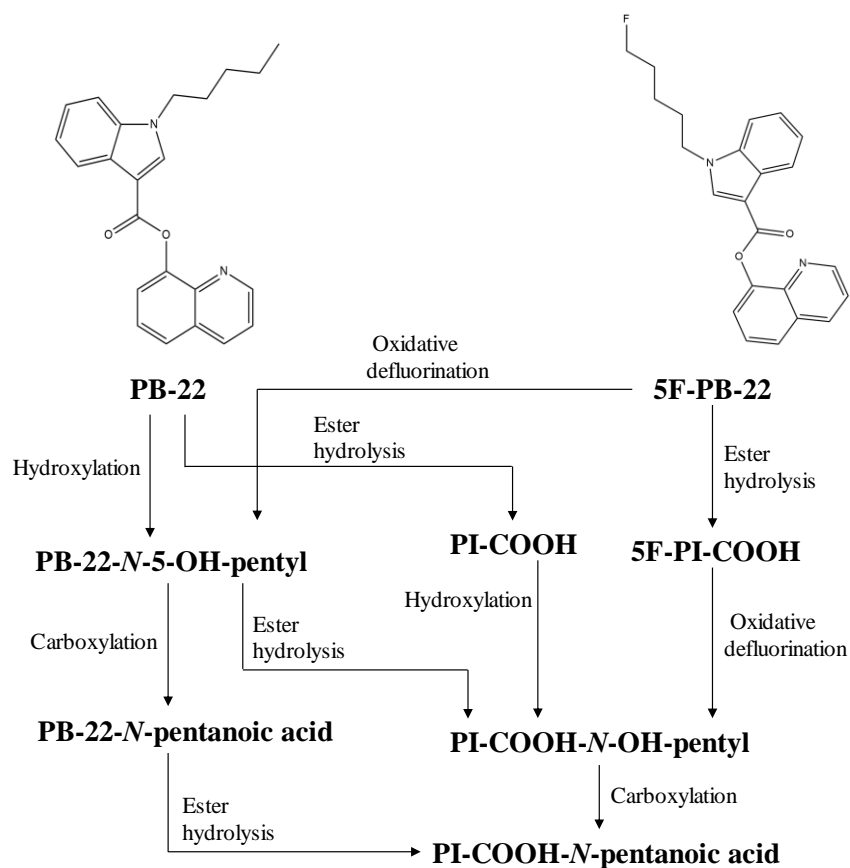


Figure 2 – Metabolic pathways for synthetic cannabinoids JWH-018, JWH-073, JWH-122, MAM-2201, PB-22 and 5F-PB-22. Ester hydrolysis of PB-22 and 5F-PB-22 produce 1-pentyl-1 H -indole-3-carboxylic acid (PI-COOH) and 5F-PI-COOH, respectively. Reproduced from (Castaneto et al., 2015).

## **AGRADECIMENTOS**

Gostaria de agradecer em primeiro lugar ao meu orientador, o Doutor Ricardo Dinis por todo o apoio prestado desde o primeiro dia na elaboração deste trabalho, pela sua prestabilidade e prontidão a ajudar sempre que precisei. Foi sem dúvida das pessoas com quem mais tive gosto em trabalhar e é um profissional exemplar.

De seguida, e porque sem o seu suporte este meu percurso nunca teria sido possível, gostaria de agradecer à minha família, especialmente aos meus pais e irmã, cujo orgulho em mim sempre foi o que me motivou a trabalhar e a ter sucesso académico.

E finalmente, porque nada na vida se faz sozinho e é preciso ter alguém ao nosso lado para nos apoiar nos momentos mais difíceis, gostaria de agradecer aos meus amigos, outro dos meus pilares neste percurso.



# **ANEXO**

**Normas de publicação Forensic Science  
International**



# FORENSIC SCIENCE INTERNATIONAL

An international journal dedicated to the applications of medicine and science in the administration of justice.

## AUTHOR INFORMATION PACK

### TABLE OF CONTENTS

•	<b>Description</b>	<b>p.1</b>
•	<b>Audience</b>	<b>p.1</b>
•	<b>Impact Factor</b>	<b>p.1</b>
•	<b>Abstracting and Indexing</b>	<b>p.2</b>
•	<b>Editorial Board</b>	<b>p.2</b>
•	<b>Guide for Authors</b>	<b>p.4</b>



ISSN: 0379-0738

### DESCRIPTION

*Forensic Science International* publishes original contributions in the many different scientific disciplines pertaining to the forensic sciences. Fields include forensic pathology and histochemistry, chemistry, biochemistry and toxicology (including drugs, alcohol, etc.), biology (including the identification of hairs and fibres), serology, odontology, psychiatry, anthropology, the physical sciences, firearms, and document examination, as well as investigations of value to public health in its broadest sense, and the important marginal area where science and medicine interact with the law.

The journal publishes: Original Research Papers (Regular Papers) Review Articles Rapid Communications Technical Notes Forensic Anthropology Population Data Case Reports Preliminary Communications Letters to the Editor Book Reviews The journal covers all legal aspects of the general disciplines listed above, as well as specialist topics of forensic interest that are included in, or are related to, these disciplines, e.g.: Biochemical and chemical analyses, and the forensic application of advanced analytical, physical, chemical and instrumental techniques Bitemark evidence Battered child syndrome Questioned documents Ballistics, projectiles and wounds Fingerprints and identification Tool marks Contact traces Poisoning Breath analysers Accident investigation and mass disasters

### AUDIENCE

Pathologists, Anthropologists, Psychiatrists, Biologists, Serologists, Odontologists, Physical Scientists, Toxicologists, Scientists in Legal and Social Medicine, Questioned Documents and Jurisprudence

### IMPACT FACTOR

2015: 1.950 © Thomson Reuters Journal Citation Reports 2016

## ABSTRACTING AND INDEXING

---

Bulletin Signalétique  
Cambridge Scientific Abstracts  
Chemical Abstracts  
Criminology, Penology and Police Science Abstracts  
Current Contents  
MEDLINE®  
EMBASE  
National Criminal Justice Reference Service  
Science Citation Index  
Biological Abstracts  
Current Awareness in Biological Sciences  
Scopus

## EDITORIAL BOARD

---

### *Co Editors-in-Chief*

**C. Cattaneo**, Dipart. di Scienze Biomediche per la Salute, Sezione di Medicina Legale, Università degli Studi di Milano, via L. Mangiagalli 37, 20133, Milano, Italy

**C. Jackowski**, Institute of Forensic Medicine, Universität Bern, Bülhlstr. 20, CH 3012, Bern, Switzerland

### *Consulting Editor-in-Chief*

**P. Saukko**, University of Turku, Turku, Finland

### *Associate Editors*

**A. Carracedo**, (for: Forensic Genetics), Institute of Legal Medicine, Universidade de Santiago de Compostela, Pedrueca 1, 39003 Santander - Cantabria, Spain

**O.H. Drummer**, (for: Toxicology), Dept. of Forensic Medicine, Monash University, Victoria, Australia

**P. Margot**, (for: Questioned Documents and Physical Science: ballistics, tool marks, contact traces, drugs analysis, fingerprints and identification etc.), Ecole des Sciences criminelles, School of Criminal Science, Université de Lausanne, bâtiment BCH, 1015 Lausanne, Switzerland

**S. Matuszewski**, (for: Forensic Entomology), Adam Mickiewicz University of Poznan, Św. Marcin 90, Poznań, Poland

### *Assistant Editors*

**A. Bécue**, (for P. Margot) Lausanne, Switzerland

**D. Deangelis**, (for C. Cattaneo) Milan, Italy

**Z. Obertova**, (for C. Cattaneo) Milan, Italy

**C. Weyermann**, (for P. Margot) Lausanne, Switzerland

### *Editorial Board*

**J. Amendt**, Frankfurt, Germany

**P. Beh**, Hong Kong, China

**P. Buzzini**, Huntsville, Texas, USA

**C. Campobasso**, Campobasso, Italy

**H. Chung**, Seoul, South Korea

**J.G. Clement**, Melbourne, VIC, Australia

**S.D. Cohle**, Grand Rapids, MI, USA

**S. Cordner**, South Melbourne, VIC, Australia

**G.L. de la Grandmaison**, Garches, France

**P. Dickens**, Buxton, UK

**H. Druid**, Stockholm, Sweden

**A. Eriksson**, Umea, Sweden

**J.A.J. Ferris**, Auckland, New Zealand

**M.C. Fishbein**, Los Angeles, CA, USA

**M.J. Hall**, London, England, UK

**C. Henssge**, Essen, Germany

**M.A. Huestis**, Baltimore, MD, USA

**H. Ikegaya**, Kyoto, Japan

**A.W. Jones**, Stockholm, Sweden

**H. Kalimo**, Helsinki, Finland

**Y. Katsumata**, Chiba, Japan

**B. Kneubuehl**, Thun, Switzerland

**G. Lau**, Singapore  
**S. Leadbeatter**, Cardiff, Wales, UK  
**C. Lennard**, Canberra, NSW, Australia  
**A. Luna Maldonado**, Murcia, Spain  
**B. Madea**, Bonn, Germany  
**H. Maeda**, Osaka, Japan  
**D. Meuwly**, The Hague, Netherlands  
**C. Neumann**, University Park, PA, USA  
**S. Pollak**, Freiburg, Germany  
**M.S. Pollanen**, Toronto, ONT, Canada  
**D.J. Pounder**, Dundee, Scotland, UK  
**K. Püschel**, Hamburg, Germany  
**G. Quatrehomme**, Nice, France  
**R. Ramotowski**, Washington, DC, USA  
**J. Robertson**, Canberra, New South Wales, Australia  
**C. Roux**, Sydney, NSW, Australia  
**I.E. Sääksjärvi**, Turku, Finland  
**J. Stevens**, Exeter, UK  
**M. Steyn**, Hatfield, South Africa  
**F. Tagliaro**, Verona, Italy  
**T. Takatori**, Chiba, Japan  
**A. Thierauf**, Freiburg, Germany  
**D. Ubelaker**, Washington, DC, USA  
**D.N. Vieira**, Coimbra, Portugal  
**J. Wells**, Miami, FL, USA  
**P. Wiltshire**, Surrey, Scotland, UK  
**X. Xu**, Shantou, Guandong Province, China  
**J. Zieba-Palus**, Kracow, Poland

## GUIDE FOR AUTHORS

---

### *Your Paper Your Way*

We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article.

**To find out more, please visit the Preparation section below.**

### INTRODUCTION

*Forensic Science International* is a peer-reviewed, international journal for the publication of original contributions in the many different scientific disciplines comprising the forensic sciences. These fields include, but are not limited to, forensic pathology and histochemistry, toxicology (including drugs, alcohol, etc.), serology, chemistry, biochemistry, biology (including the identification of hairs and fibres), odontology, psychiatry, anthropology, the physical sciences, firearms, and document examination, as well as the many other disciplines where science and medicine interact with the law.

### *Types of paper*

1. Original Research Articles (Regular Papers)
2. Review Articles
3. Rapid Communications
4. Technical Notes
5. Forensic Anthropology Population Data
6. Case Reports
7. Preliminary Communications
8. Letters to the Editor
9. Book Reviews

Please note that all contributions of type 4 to 7 will be published as e-only articles. Their citation details, including e-page numbers, will continue to be listed in the relevant print issue of the journal's Table of Contents.

**Announcement of Population Data:** these types of articles will be published in *Forensic Science International: Genetics*, only. Please submit these articles via <http://www.ees.elsevier.com/fsigen/>.

**Preliminary Communications** (where brief accounts of important new work may be announced with less delay than is inevitable with major papers) may be accepted after correspondence with the appropriate Associate Editor.

**Review Articles** may be regularly submitted or invited by Editors. However, they will undergo the normal review process of the journal.

**Forensic Anthropology Population Data:** Although the main focus of the anthropology section of the journal remains on the publication of original research, authors are invited to submit their forensic anthropology population data articles by selecting the "Forensic Anthropology Population Data" article type on the online submission system. When submitting a Forensic Anthropology Population data article, please assure that "Forensic Anthropology Population Data" is included as one of the keywords. These forensic anthropology population data articles involve the application of already published and standardised methods of aging, sexing, determination of ancestry and stature and other well known diagnoses on different populations. This is at the heart of applied forensic anthropology. For example, in order to correctly assess age, stature or even sex of individuals of different ancestry or from different populations, it is fundamental that the method be tested on the specific population one is working on. In building the biological profile of a skeleton in order to aid identification, one needs to calibrate such techniques on the population of interest before applying them. The same may be true in a completely different scenario of anthropology, for example identifying criminals taped on video surveillance systems and aging victims of juvenile pornography. This section is dedicated to forensic anthropological population data and other types of updates (state of the art of particular issues, etc.), particularly concerning the following:

- Sexing

- Aging sub adult skeletal remains
- Aging adult skeletal remains
- Aging living sub adults and adults
- Determining ancestry
- Stature estimation
- Facial reconstruction
- Non metric trait distribution, pathology and trauma
- Positive identification of human skeletal remains
- Positive identification of the living

Forensic Anthropology Population Data articles will be published in abridged form in print (a clear, descriptive summary taken from the abstract), and the full length article will be published online only. Full citation details and a reference to the online article, including e-page numbers, will be published in the relevant print issue of the journal. All submitted manuscripts will be evaluated by a strict peer review process.

**Case Reports** will be accepted only if they contain some important new information for the readers.

**Rapid Communications** should describe work of significant interest, whose impact would suffer if publication were not expedited. They should not be longer than 5 printed journal pages (about 10 submitted pages). Authors may suggest that their work is treated as a Rapid Communication, but the final decision on whether it is suitable as such will be taken by the handling Editor. Rapid Communications requiring revision should be resubmitted as a new submission.

**Technical Notes** report new developments, significant advances and novel aspects of experimental and theoretical methods and techniques which are relevant for scientific investigations within the journal scope. Manuscripts of this type should be short (a few pages only). Highly detailed and specific technical information such as computer programme code or user manuals can be included as electronic supplements. The manuscript title must start with "Technical Note:".

### **Revisions deadline**

Please note that articles that are sent to the author for revision need to be returned within 60 days (and within 20 days for subsequent revisions). A reminder will be sent in the second month. Any articles that are sent after the two month period of revision will be considered a re-submission.

### **Contact details for submission**

Papers for consideration should be submitted by topic. Editors and their topic specialty are listed below.

**C. Cattaneo** (Co Editors-in-Chief):

Tel: +39 02503 15679

E-mail: cristina.cattaneo@unimi.it

**C. Jackowski** (Co Editors-in-Chief):

Tel: +41 (0)31 631 84 12

E-mail: Christian.Jackowski@irm.unibe.ch

**A. Carracedo:** Forensic Genetics. Please note only review articles on this topic should be submitted to FSI. All non-review papers should be submitted to the FSI daughter journal devoted to this subject Forensic Science International: Genetics, via <http://ees.elsevier.com/fsigen/>

Fax: +34 981 580336

E-mail: angel.carrafsi@usc.es

**P. Margot:** Questioned Documents and Physical Science: ballistics, tool marks, contact traces, drugs analysis, fingerprints and identification, etc.

Tel: +41 21 692 4605

Fax: +41 21 692 4605

E-mail: pierre.margot@unil.ch

**O.H. Drummer:** Toxicology

Tel: +61 3 9684 4334

Fax: +61 3 9682 7353  
E-mail: [olaf.drummer@vifm.org](mailto:olaf.drummer@vifm.org)

**S. Matuszewski:** Entomology  
Tel: +48 61 82 94 292  
E-Mail: [szymmat@amu.edu.pl](mailto:szymmat@amu.edu.pl)

### **Submission checklist**

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

#### **Ensure that the following items are present:**

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address

All necessary files have been uploaded:

*Manuscript:*

- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Indicate clearly if color should be used for any figures in print

*Graphical Abstracts / Highlights files* (where applicable)

*Supplemental files* (where applicable)

Further considerations

- Manuscript has been 'spell checked' and 'grammar checked'
- All references mentioned in the Reference List are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Internet)
- Relevant declarations of interest have been made
- Journal policies detailed in this guide have been reviewed
- Referee suggestions and contact details provided, based on journal requirements

For further information, visit our [Support Center](#).

#### **BEFORE YOU BEGIN**

##### **Ethics in publishing**

Please see our information pages on [Ethics in publishing](#) and [Ethical guidelines for journal publication](#).

##### **Declaration of interest**

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. [More information](#).

##### **Additional information**

Multiple submissions is not acceptable to the Editor, and any such papers, together with future submissions from the authors, will be rejected outright. Submission also implies that all authors have approved the paper for release and are in agreement with its content.

##### **Submission declaration and verification**

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see '[Multiple, redundant or concurrent publication](#)' section of our ethics policy for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify originality, your article may be checked by the originality detection service [CrossCheck](#).

## Contributors

Each author is required to declare his or her individual contribution to the article: all authors must have materially participated in the research and/or article preparation, so roles for all authors should be described. The statement that all authors have approved the final article should be true and included in the disclosure.

## Changes to authorship

Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the **corresponding author**: (a) the reason for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.

Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of authors **after** the manuscript has been accepted. While the Editor considers the request, publication of the manuscript will be suspended. If the manuscript has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

### Article transfer service

This journal is part of our Article Transfer Service. This means that if the Editor feels your article is more suitable in one of our other participating journals, then you may be asked to consider transferring the article to one of those. If you agree, your article will be transferred automatically on your behalf with no need to reformat. Please note that your article will be reviewed again by the new journal.

[More information.](#)

## Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see [more information](#) on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. [Permission](#) of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has [preprinted forms](#) for use by authors in these cases.

For open access articles: Upon acceptance of an article, authors will be asked to complete an 'Exclusive License Agreement' ([more information](#)). Permitted third party reuse of open access articles is determined by the author's choice of [user license](#).

## Author rights

As an author you (or your employer or institution) have certain rights to reuse your work. [More information.](#)

### Elsevier supports responsible sharing

Find out how you can [share your research](#) published in Elsevier journals.

## Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

### Funding body agreements and policies

Elsevier has established a number of agreements with funding bodies which allow authors to comply with their funder's open access policies. Some funding bodies will reimburse the author for the Open Access Publication Fee. Details of [existing agreements](#) are available online.



After acceptance, open access papers will be published under a noncommercial license. For authors requiring a commercial CC BY license, you can apply after your manuscript is accepted for publication.

### Open access

This journal offers authors a choice in publishing their research:

#### Open access

- Articles are freely available to both subscribers and the wider public with permitted reuse.
- An open access publication fee is payable by authors or on their behalf, e.g. by their research funder or institution.

#### Subscription

- Articles are made available to subscribers as well as developing countries and patient groups through our [universal access programs](#).
- No open access publication fee payable by authors.

Regardless of how you choose to publish your article, the journal will apply the same peer review criteria and acceptance standards.

For open access articles, permitted third party (re)use is defined by the following [Creative Commons user licenses](#):

*Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)*

For non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

The open access publication fee for this journal is **USD 2500**, excluding taxes. Learn more about Elsevier's pricing policy: <http://www.elsevier.com/openaccesspricing>.

#### Green open access

Authors can share their research in a variety of different ways and Elsevier has a number of green open access options available. We recommend authors see our [green open access page](#) for further information. Authors can also self-archive their manuscripts immediately and enable public access from their institution's repository after an embargo period. This is the version that has been accepted for publication and which typically includes author-incorporated changes suggested during submission, peer review and in editor-author communications. Embargo period: For subscription articles, an appropriate amount of time is needed for journals to deliver value to subscribing customers before an article becomes freely available to the public. This is the embargo period and it begins from the date the article is formally published online in its final and fully citable form. [Find out more](#).

This journal has an embargo period of 12 months.

#### Elsevier Publishing Campus

The Elsevier Publishing Campus ([www.publishingcampus.com](http://www.publishingcampus.com)) is an online platform offering free lectures, interactive training and professional advice to support you in publishing your research. The College of Skills training offers modules on how to prepare, write and structure your article and explains how editors will look at your paper when it is submitted for publication. Use these resources, and more, to ensure that your submission will be the best that you can make it.

#### Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the [English Language Editing service](#) available from Elsevier's WebShop.

### Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

#### Submit your article

Please submit your article via <http://ees.elsevier.com/fsi>.

## PREPARATION

### NEW SUBMISSIONS

Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts your files to a single PDF file, which is used in the peer-review process.

As part of the Your Paper Your Way service, you may choose to submit your manuscript as a single file to be used in the refereeing process. This can be a PDF file or a Word document, in any format or layout that can be used by referees to evaluate your manuscript. It should contain high enough quality figures for refereeing. If you prefer to do so, you may still provide all or some of the source files at the initial submission. Please note that individual figure files larger than 10 MB must be uploaded separately.

#### *References*

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct.

#### *Formatting requirements*

There are no strict formatting requirements but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions.

If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes.

Divide the article into clearly defined sections.

#### *Figures and tables embedded in text*

Please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file. The corresponding caption should be placed directly below the figure or table.

### Double-blind review

This journal uses double-blind review, which means the identities of the authors are concealed from the reviewers, and vice versa. [More information](#) is available on our website. To facilitate this, please include the following separately:

*Title page (with author details):* This should include the title, authors' names and affiliations, and a complete address for the corresponding author including an e-mail address.

*Blinded manuscript (no author details):* The main body of the paper (including the references, figures, tables and any acknowledgements) should not include any identifying information, such as the authors' names or affiliations.

### REVISED SUBMISSIONS

#### *Use of word processing software*

Regardless of the file format of the original submission, at revision you must provide us with an editable file of the entire article. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the [Guide to Publishing with Elsevier](#)). See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

### Article structure

#### *Introduction*

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

#### *Material and methods*

Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described.

#### *Results*

Results should be clear and concise.

### *Discussion*

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

### *Conclusions*

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

### **Essential title page information**

- **Title.** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
- **Author names and affiliations.** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- **Corresponding author.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
- **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

### **Abstract**

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

### *Graphical abstract*

Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view [Example Graphical Abstracts](#) on our information site.

Authors can make use of Elsevier's Illustration and Enhancement service to ensure the best presentation of their images and in accordance with all technical requirements: [Illustration Service](#).

### *Highlights*

Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). You can view [example Highlights](#) on our information site.

### **Keywords**

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

### *Acknowledgements*

Please provide Acknowledgements as a separate file and remove this from the manuscript. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

### *Formatting of funding sources*

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

#### *Footnotes*

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article.

### **Artwork**

#### *Electronic artwork*

##### *General points*

- Make sure you use uniform lettering and sizing of your original artwork.
- Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Indicate per figure if it is a single, 1.5 or 2-column fitting image.
- For Word submissions only, you may still provide figures and their captions, and tables within a single file at the revision stage.
- Please note that individual figure files larger than 10 MB must be provided in separate source files. A detailed [guide on electronic artwork](#) is available.

**You are urged to visit this site; some excerpts from the detailed information are given here.**

#### *Formats*

Regardless of the application used, when your electronic artwork is finalized, please 'save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings. Embed the font or save the text as 'graphics'.

TIFF (or JPG): Color or grayscale photographs (halftones): always use a minimum of 300 dpi.

TIFF (or JPG): Bitmapped line drawings: use a minimum of 1000 dpi.

TIFF (or JPG): Combinations bitmapped line/half-tone (color or grayscale): a minimum of 500 dpi is required.

#### **Please do not:**

- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); the resolution is too low.
- Supply files that are too low in resolution.
- Submit graphics that are disproportionately large for the content.

#### *Color artwork*

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article.** Please indicate your preference for color: in print or online only. [Further information on the preparation of electronic artwork.](#)

#### *Figure captions*

Ensure that each illustration has a caption. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

## Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

## References

### *Citation in text*

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

### *Reference links*

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is encouraged.

A DOI can be used to cite and link to electronic articles where an article is in-press and full citation details are not yet known, but the article is available online. A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. *Journal of Geophysical Research*, <http://dx.doi.org/10.1029/2001JB000884i>. Please note the format of such citations should be in the same style as all other references in the paper.

### *Data references*

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

### *Reference management software*

Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support [Citation Style Language styles](#), such as [Mendeley](#) and [Zotero](#), as well as [EndNote](#). Using the word processor plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal's style. If no template is yet available for this journal, please follow the format of the sample references and citations as shown in this Guide.

Users of Mendeley Desktop can easily install the reference style for this journal by clicking the following link:

<http://open.mendeley.com/use-citation-style/forensic-science-international>

When preparing your manuscript, you will then be able to select this style using the Mendeley plug-ins for Microsoft Word or LibreOffice.

### *Reference formatting*

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct. If you do wish to format the references yourself they should be arranged according to the following examples:



### Reference style

**Text:** Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.

Example: '..... as demonstrated [3,6]. Barnaby and Jones [8] obtained a different result ....'

**List:** Number the references (numbers in square brackets) in the list in the order in which they appear in the text.

### Examples:

Reference to a journal publication:

[1] J. van der Geer, J.A.J. Hanraads, R.A. Lupton, The art of writing a scientific article, *J. Sci. Commun.* 163 (2010) 51–59.

Reference to a book:

[2] W. Strunk Jr., E.B. White, *The Elements of Style*, fourth ed., Longman, New York, 2000.

Reference to a chapter in an edited book:

[3] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), *Introduction to the Electronic Age*, E-Publishing Inc., New York, 2009, pp. 281–304.

Reference to a website:

[4] Cancer Research UK, Cancer statistics reports for the UK. <http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/>, 2003 (accessed 13.03.03).

Reference to a dataset:

[dataset] [5] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1, 2015. <http://dx.doi.org/10.17632/xwj98nb39r.1>.

### Video

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the files in one of our recommended file formats with a preferred maximum size of 150 MB. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including [ScienceDirect](#). Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our [video instruction pages](#). Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

### Supplementary material

Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

### Data in Brief

You have the option of converting any or all parts of your supplementary or additional raw data into one or multiple data articles, a new kind of article that houses and describes your data. Data articles ensure that your data is actively reviewed, curated, formatted, indexed, given a DOI and publicly available to all upon publication. You are encouraged to submit your article for *Data in Brief* as an additional item directly alongside the revised version of your manuscript. If your research article is accepted, your data article will automatically be transferred over to *Data in Brief* where it will be editorially reviewed and published in the open access data journal, *Data in Brief*. Please note an open access fee is payable for publication in *Data in Brief*. Full details can be found on the [Data in Brief website](#). Please use [this template](#) to write your Data in Brief.

## AudioSlides

The journal encourages authors to create an AudioSlides presentation with their published article. AudioSlides are brief, webinar-style presentations that are shown next to the online article on ScienceDirect. This gives authors the opportunity to summarize their research in their own words and to help readers understand what the paper is about. [More information and examples are available](#). Authors of this journal will automatically receive an invitation e-mail to create an AudioSlides presentation after acceptance of their paper.

## AFTER ACCEPTANCE

### *Availability of accepted article*

This journal makes articles available online as soon as possible after acceptance. This concerns the accepted article (both in HTML and PDF format), which has not yet been copyedited, typeset or proofread. A Digital Object Identifier (DOI) is allocated, thereby making it fully citable and searchable by title, author name(s) and the full text. The article's PDF also carries a disclaimer stating that it is an unedited article. Subsequent production stages will simply replace this version.

### Online proof correction

Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors.

If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.

We will do everything possible to get your article published quickly and accurately. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

### Offprints

The corresponding author will, at no cost, receive 25 free paper offprints, or alternatively a customized [Share Link](#) providing 50 days free access to the final published version of the article on [ScienceDirect](#). The Share Link can be used for sharing the article via any communication channel, including email and social media. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's [Webshop](#). Corresponding authors who have published their article open access do not receive a Share Link as their final published version of the article is available open access on ScienceDirect and can be shared through the article DOI link.

### Author orders

When your article is published, you can commemorate your publication with printed author copies of the journal issue, customized full-color posters, extra offprints, and more. Please visit <http://webshop.elsevier.com> to learn more.

## AUTHOR INQUIRIES

Visit the [Elsevier Support Center](#) to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.

You can also [check the status of your submitted article](#) or find out [when your accepted article will be published](#).

© Copyright 2014 Elsevier | <http://www.elsevier.com>